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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/703,253	10/31/2000	Marrie Harras	LEX-0081-USA	1776

7590

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EXAMINER

LANDSMAN, ROBERT

ART UNIT

PAPER NUMBER

1647

DATE MAILED: 12/19/2001

Please find below and/or attached an Office communication concerning this application or proceeding.

**Office Action Summary**

Application No.

09/703,253

Applicant(s)

HARRAS ET AL.

Examiner

Robert Landsman

Art Unit

1647

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --  
**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 13 August 2001.
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1-4 is/are pending in the application.
- 4a) Of the above claim(s) 3 and 4 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1 and 2 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☒ Claim(s) 1-4 are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on \_\_\_\_\_ is: a) ☐ approved b) ☐ disapproved by the Examiner.  
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).  
a) ☐ All b) ☐ Some \* c) ☐ None of:  
1. ☐ Certified copies of the priority documents have been received.  
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.  
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).  
\* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).  
a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

- 1) ☒ Notice of References Cited (PTO-892)                      4) ☐ Interview Summary (PTO-413) Paper No(s). \_\_\_\_\_
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)                      5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 8, 10.                      6) ☒ Other: *Sequence Comparison A*.

Art Unit: 1647

## DETAILED ACTION

### 1. Election/Restriction

A. Restriction to one of the following inventions is required under 35 U.S.C. 121:

- I. Claims 1 and 2, drawn to an isolated nucleic acid molecule of SEQ ID NO:23 and encoding SEQ ID NO:24, classified in class 536, subclass 23.5.
- II. Claim 3, drawn to an isolated nucleic acid molecule of SEQ ID NO:1 and encoding SEQ ID NO:2, classified in class 536, subclass 23.5.
- III. Claim 4, drawn to an isolated nucleic acid molecule of SEQ ID NO:47 and encoding SEQ ID NO:48, classified in class 536, subclass 23.5.

B. The inventions are distinct, each from each other because of the following reasons:

Inventions I-III are independent and distinct, each from each other, because they are products which possess characteristic differences in structure and function and each has an independent utility that is distinct for each invention which cannot be exchanged.

Because these inventions are distinct for the reasons given above and have acquired a separate status in the art as shown by their different classification and recognized divergent subject matter as defined by MPEP § 808.02, the Examiner has *prima facie* shown a serious burden of search (see MPEP § 803). Therefore, an initial requirement of restriction for examination purposes as indicated is proper.

C. A telephone call was made to David Hibler on November 20, 2001 to request an oral election to the above restriction. Applicant's election of Group I is acknowledged with traverse. Therefore, Group I (claims 1 and 2) will be examined in the present application.

Art Unit: 1647

Applicant is reminded that upon cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR § 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a diligently-filed petition under 37 CFR § 1.48(b) and by the fee required under 37 CFR § 1.17 (h).

## ***2. Oath/Declaration***

A. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02. The oath or declaration is defective because: Non-initialed and/or non-dated alterations have been made to the oath or declaration. See 37 CFR 1.52(c).

## ***3. Claim Rejections - 35 USC § 101***

35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

A. Claims 1 and 2 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by a specific, substantial and credible asserted utility or a well established utility. These claims are drawn to an invention with no apparent or disclosed patentable utility. Applicants have only disclosed that the polynucleotide and the encoded polypeptide of the invention are believed to encode novel human proteins (NHPs) which share structural similarity to multi-drug resistance proteins (MDRs).

However, it is clear from the instant specification that the claimed receptor is termed an "orphan receptor" in the art. The instant application does not disclose the biological role of the claimed protein or its significance. There is little doubt that, after complete characterization, this protein will probably be

Art Unit: 1647

found to have a patentable utility. This further characterization, however, is part of the act of invention and, until it has been undertaken, Applicants' claimed invention is incomplete.

The instant situation is directly analogous to that of which was addressed in *Brenner v. Manson*, 148 U.S.P.Q. 689 (Sus. Ct, 1966), in which a novel compound which was structurally analogous to other compounds which were known to possess anticancer activity was alleged to be potentially useful as an antitumor agent in the absence of evidence supporting this utility. The court expressed the opinion that all chemical compounds are "useful" to the chemical arts when this term is given its broadest interpretation. However, the court held that this broad interpretation was not the intended definition of "useful" as it appears in 35 U.S.C. 101, which required that an invention must have either an immediate obvious or fully disclosed "real-world" utility. The court held that:

"The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility," "[u]nless and until a process is refined and developed to this point - where specific benefit exists in currently available form - there is insufficient justification for permitting an applicant to engross what may prove to be a broad field," and "a patent is not a hunting license," "[i]t is not a reward for the search, but compensation for its successful conclusion."

The specification discloses that the polynucleotides of the invention encode proteins which have significant sequence similarity to known MDR proteins. Based on the structural similarity, the specification asserts that the newly disclosed SEQ ID NO:23 and 24 have similar activities. The assertion that the disclosed proteins have biological activities similar to known MDRs cannot be accepted in the absence of supporting evidence, because the relevant literature reports examples of polypeptide families wherein individual members have distinct, and sometimes even opposite, biological activities.

In the transforming growth factor (TGF) family, Vukicevic et al. (1996, PNAS USA 93:9021-9026) disclose that OP-1, a member of the TGF- family of proteins, has the ability to induce metanephrogenesis, whereas closely related TGF- family members BMP-2 and TGF- 1 had no effect on metanephrogenesis under identical conditions (p. 9023, paragraph bridging columns 1-2). See also Massague, who reviews other members of the TGF- family (1987, Cell 49:437-8, esp. p. 438, column 1,

Art Unit: 1647

second full paragraph to the end). Similarly, PTH and PTHrP are two structurally closely related proteins which can have opposite effects on bone resorption (Pilbeam et al., 1993, Bone 14:717-720; see p. 717, second paragraph of Introduction). Finally, Kopchick et al. (U.S. Patent 5,350,836) disclose several antagonists of vertebrate growth hormone that differ from naturally occurring growth hormone by a single amino acid (column 2, lines 37-48).

Generally, the art acknowledges that function cannot be predicted based solely on structural similarity to a protein found in the sequence databases. For example, Skolnick et al. (2000, Trends in Biotech. 18:34-39) state that knowing the protein structure by itself is insufficient to annotate a number of functional classes, and is also insufficient for annotating the specific details of protein function (see Box 2, p. 36). Similarly, Bork (2000, Genome Research 10:398-400) states that the error rate of functional annotations in the sequence database is considerable, making it even more difficult to infer correct function from a structural comparison of a new sequence with a sequence database (see especially p. 399). Such concerns are also echoed by Doerks et al. (1998, Trends in Genetics 14:248-250) who state that (1) functional information is only partially annotated in the database, ignoring multi functionality, resulting in underpredictions of functionality of a new protein and (2) overpredictions of functionality occur because structural similarity often does not necessarily coincide with functional similarity. Smith et al. (1997, Nature Biotechnology 15:1222-1223) remark that there are numerous cases in which proteins having very different functions share structural similarity due to evolution from a common ancestral gene.

Brenner (1999, Trends in Genetics 15:132-133) argues that accurate inference of function from homology must be a difficult problem since, assuming there are only about 1000 major gene superfamilies in nature, then most homologs must have different molecular and cellular functions. Finally, Bork et al. (1996, Trends in Genetics 12:425-427) add that the software robots that assign functions to new proteins often assign a function to a whole new protein based on structural similarity of a

Art Unit: 1647

small domain of the new protein to a small domain of a known protein. Such questionable interpretations are written into the sequence database and are then considered facts.

Therefore, based on the discussions above concerning the specific examples of structurally similar proteins that have different functions, along with the art's recognition that one cannot rely upon structural similarity alone to determine functionality, the specification fails to teach the skilled artisan the utility of the claimed polynucleotides of SEQ ID NO:23 which are only known to be homologous to MDRs. Therefore, the instant claims are drawn to a polynucleotide encoding a protein which has a yet undetermined function or biological significance. There is no actual and specific significance which can be attributed to said protein identified in the specification. For this reason, the instant invention is incomplete. In the absence of a knowledge of the natural ligands or biological significance of this protein, there is no immediately obvious patentable use for it. To employ a protein of the instant invention in the identification of substances which bind to and/or mediate activity of the said receptor is clearly to use it as the object of further research which has been determined by the courts to be a non-patentable utility. Since the instant specification does not disclose a "real-world" use for said protein then the claimed invention is incomplete and, therefore, does not meet the requirements of 35 U.S.C. 101 as being useful.

#### ***4. Claim Rejections - 35 USC § 112, first paragraph - enablement***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

A. Claims 1 and 2 are rejected under 35 U.S.C. 112, first paragraph, as failing to adequately teach how to use the instant invention. Specifically, since the claimed invention is not supported by a specific, substantial and credible asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Art Unit: 1647

B. Claim 2 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

In In re Wands, 8USPQ2d, 1400 (CAFC 1988) page 1404, the factors to be considered in determining whether a disclosure would require undue experimentation include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

First, the breadth of the claims is excessive with regard to claiming all nucleic acid molecules which “hybridize” under stringent conditions to SEQ ID NO:23, or which comprise “at least 24 contiguous bases of SEQ ID NO:23. Nucleic acid molecules which “hybridize” to SEQ ID NO:23 would have one or more nucleic acid substitutions, deletions, insertions and/or additions to SEQ ID NO:23. Furthermore, Applicants have not demonstrated that the sequences of the present invention, SEQ ID NO:23 or 24, have a utility. Since Applicants have not taught how to use the nucleic acid molecule of claim 23, or the protein of claim 24, they have, therefore, also not taught how to use nucleic acid molecules which hybridize to SEQ ID NO:23, or the encoded proteins, nor have they taught the artisan how to use molecules of “at least 24 contiguous bases” of SEQ ID NO:23. Applicants provide no guidance or working examples of nucleic acid molecules which hybridize to SEQ ID NO:23, nor do they provide a *function* of these nucleic acid molecules, or of the proteins which they encode. Furthermore, it is not predictable to one of ordinary skill in the art what the functions of these nucleic acids, or the proteins which they encode, are.

In summary, the breadth of the claims is excessive with regard to Applicants claiming all nucleic acids which hybridize to SEQ ID NO:23, or to molecules of “at least 24 contiguous bases” of SEQ ID NO:23. There is also a lack of guidance and working examples of these nucleic acid molecules.



Art Unit: 1647

Applicants do not provide a function of these nucleic acid molecules, or a function of the proteins which they encode. These factors, along with the lack of predictability to one of ordinary skill in the art as to what the functions of these nucleic acids are, or the proteins which they encode are leads the Examiner to hold that undue experimentation is necessary to practice the invention as claimed.

***5. Claim Rejections - 35 USC § 112, first paragraph – written description***

A. Claims and are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

These are genus claims. Nucleic acid molecules which “**hybridize**” to those polynucleotides encoding SEQ ID NO:23 would have one or more nucleic acid substitutions, deletions, insertions and/or additions to said polynucleotides which would also encode for a protein with one or more amino acid substitutions, deletions, insertions and/or additions to the protein encoded for by SEQ ID NO:24.

The specification and claims do not indicate what distinguishing attributes are shared by the members of the genus. Thus the scope of the claims includes numerous structural variants, and the genus is highly variant because a significant number of structural differences between genus members is permitted. Although these types of changes are routinely done in the art, the specification and claims do not provide any guidance as to what changes should be made. Structural features that could distinguish compounds in the genus from others in the nucleic acid or protein class are missing from the disclosure. No common structural attributes identify the members of the genus. The general knowledge and level of skill in the art do not supplement the omitted description because specific, not general, guidance is what is needed. Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus, and because the genus is highly variant, SEQ ID NO:23 and 24, or molecules which hybridize to SEQ ID NO:23 (which could be at least thousands of molecules) alone are insufficient to describe the

Art Unit: 1647

genus. One of skill in the art would reasonable conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus at the time the invention was made.

Furthermore, the specification provides a written description of only one nucleic acid construct (SEQ ID NO:23). No other species are described, or structurally contemplated, within the instant specification. Therefore, one skilled in the art cannot reasonably visualize or predict critical nucleic acid residues which would structurally characterize the genus of nucleic acids encoding the genus of NHPs claimed, because it is unknown and not described what structurally constitutes any different nucleic acids encoding NHPs or nucleic acids encoding NHPs from any different species, which are further not described, or any different nucleic acid sequence which "hybridizes" to, or which comprise "at least 24 contiguous bases of", SEQ ID NO:23, or any nucleotide sequence that encompasses unknown and undescribed promotor sequences, introns, allelic variants, or other sequences "comprising" at least 24 contiguous bases of SEQ ID NO:23, or those molecules which hybridize to SEQ ID NO:23; thereby not meeting the written description requirement under 35 USC 112, first paragraph.

***6. Claim Rejections - 35 USC § 112, second paragraph***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

A. Claim 2 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. This claim is vague and indefinite since the claim recites "stringent conditions." It is not known what these conditions are. Nucleic acid molecules which hybridize under conditions of "low" stringency would not necessarily hybridize under conditions of "high" stringency. Furthermore, not all conditions of "high" or "low" stringency, for example, are the same. Therefore, it is required that Applicants amend the claims

Art Unit: 1647

to recite the **exact** hybridization conditions without using indefinite phrases such as "*for example*" **without adding new matter.**

**7. Claim Rejections - 35 USC § 102**

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

A. Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by Suzuki et al. (BBRC 238:790-794, 1997). The claim recites an isolated nucleic acid molecule comprising nucleotide sequence that hybridizes under stringent conditions to SEQ ID NO:23. Suzuki et al. teach a nucleic acid molecule which has numerous regions of contiguous bases which are 100% identical to SEQ ID NO:23. These regions comprise anywhere from 9 to up to 14 contiguous bases. Therefore, even under high stringency conditions, the molecule of Suzuki et al. meets the limitation of the claim.

**Advisory information**

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert Landsman whose telephone number is (703) 306-3407. The examiner can normally be reached on Monday - Friday from 8:00 AM to 5:00 PM (Eastern time) and alternate Fridays from 8:00 AM to 5:00 PM (Eastern time).

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Gary Kunz, can be reached on (703) 308-4623.

Official papers filed by fax should be directed to (703) 308-4242. Fax draft or informal communications with the examiner should be directed to (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Robert Landsman, Ph.D.  
Patent Examiner  
Group 1600  
December 17, 2001

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